Pharmacology Biochemistry & Behavior, Vol. 25, pp. 293–296, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

The Effect of Magnocellular Basal Forebrain Lesions on Circadian Locomotor Activity in the Rat[1]

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HEPLER, D. J. AND B. E. LERER. *The effect of magnocellular basal forebrain lesions on circadian locomotor activity in the rat.* PHARMACOL BIOCHEM BEHAV 25(1) 293–296, 1986.—Locomotor activity (LMA) was assessed in rats given ibotenic acid lesions in the nucleus basalis magnocellularis (group NBM) or sham surgery (group OC). Two weeks after surgery, rats were monitored for 8 hours during the middle of either the 12 hr light (day) or 12 hr dark (night) period of the diurnal cycle. Six behavioral measures of LMA were examined: horizontal activity, vertical activity (rearing), distance travelled, movement time, movement velocity (distance/time) and revolutions (turning behavior). During the day, no statistically significant differences between the NBM and OC groups were observed in any of the measures. At night, both NBM and OC groups generally were more active than during the day, and the NBM group generally was more active than the OC group. Because the diurnal LMA of rats with NBM lesions was not significantly affected during the day, when laboratory animals are usually tested, hypotheses regarding lesion-induced locomotor abnormalities cannot be invoked to account entirely for the impaired performance observed in NBM rats on tasks designed to measure learning and memory.

Nucleus basalis magnocellularis Locomotor activity Diurnal cycle Memory

EXCITOTOXIC lesions of the rat nucleus basalis magnocellularis (NBM) produce cortical cholinergic hypofunction and behavioral impairments [3, 5–7] which approximate the cholinergic and cognitive dysfunction of Alzheimer's disease (AD). Although the behavioral impairments, which are observed in both appetitively- and aversively-motivated tasks, are suggestive of learning and memory dysfunction, certain of these impairments may result from adjunctive changes in motor activity or other non-cognitive factors such as shock hypersensitivity. Hippocampal lesions, for example, enhance the acquisition of an active avoidance task [1,4]; however, this does not imply necessarily that hippocampal lesions improve learning. Rather, the lesion produces hyperactivity [11] and increased shock sensitivity [2] and these, in turn, may facilitate avoidance acquisition. Similarly, in studies of NBM lesion effects, non-associative factors must be ruled out as sources of behavioral variation before impaired performance can be attributed to a cognitive defect resulting from lesion-induced cholinergic hypofunction.

Previous research indicates that the NBM lesion does not significantly impair shock sensitivity, motivation or sensorimotor processes [3, 5–7] although it may produce a tendency towards increased locomotor activity (LMA). Preliminary research in our own laboratory showed that NBM lesions produced small but significant increases in LMA for the first 20 min of a 30 min test period. Recently, Sanberg *et al.* [9] reported that kainic acid lesions of the striatum produce nighttime hyperactivity without daytime activity changes. The present experiment was designed to determine whether similar changes result from NBM lesions, and to provide a more detailed description of the effects of NBM lesions on LMA than has been previously available.

METHOD

Forty-eight male Sprague-Dawley rats (180–220 g) were group-housed with free access to food and water, and kept on a 12:12 light/dark cycle with lights on at 0700 hr. Half the subjects (group NBM) received bilateral NBM lesions made with 0.6 μl injections of 67 nM ibotenic acid (Sigma, St. Louis, MO) at coordinates of 0.7 mm posterior to bregma, 2.7 mm lateral to the midsagittal suture, and 7.0 mm ventral to dura; the remaining subjects were sham-operated controls (group OC). Following a two week recovery period, LMA was assessed in Digiscan animal-activity monitors (Omnitech Model RXYZCM16). Each rat was tested for 9–14 hr during either the light or dark period of the diurnal cycle in an acrylic cage (40×40×30.5 cm) with continuously available food and water. The data from the middle 8 hr of each period (0900–1700 or 2100–0500 hr) were collected in one-hour bins and processed by a Digiscan Analyzer (Omnitech Model DCM-8), stored on a DEC PDP 11/73 computer, and post-processed with RS/1 (BBN Research Systems, Cambridge,

[1]Portions of this paper were presented at the symposium on "Locomotor Behavior: Neuropharmacological Substrates of Motor Activation," 15th Annual Society for Neuroscience meeting, Dallas, TX, October 20, 1985.

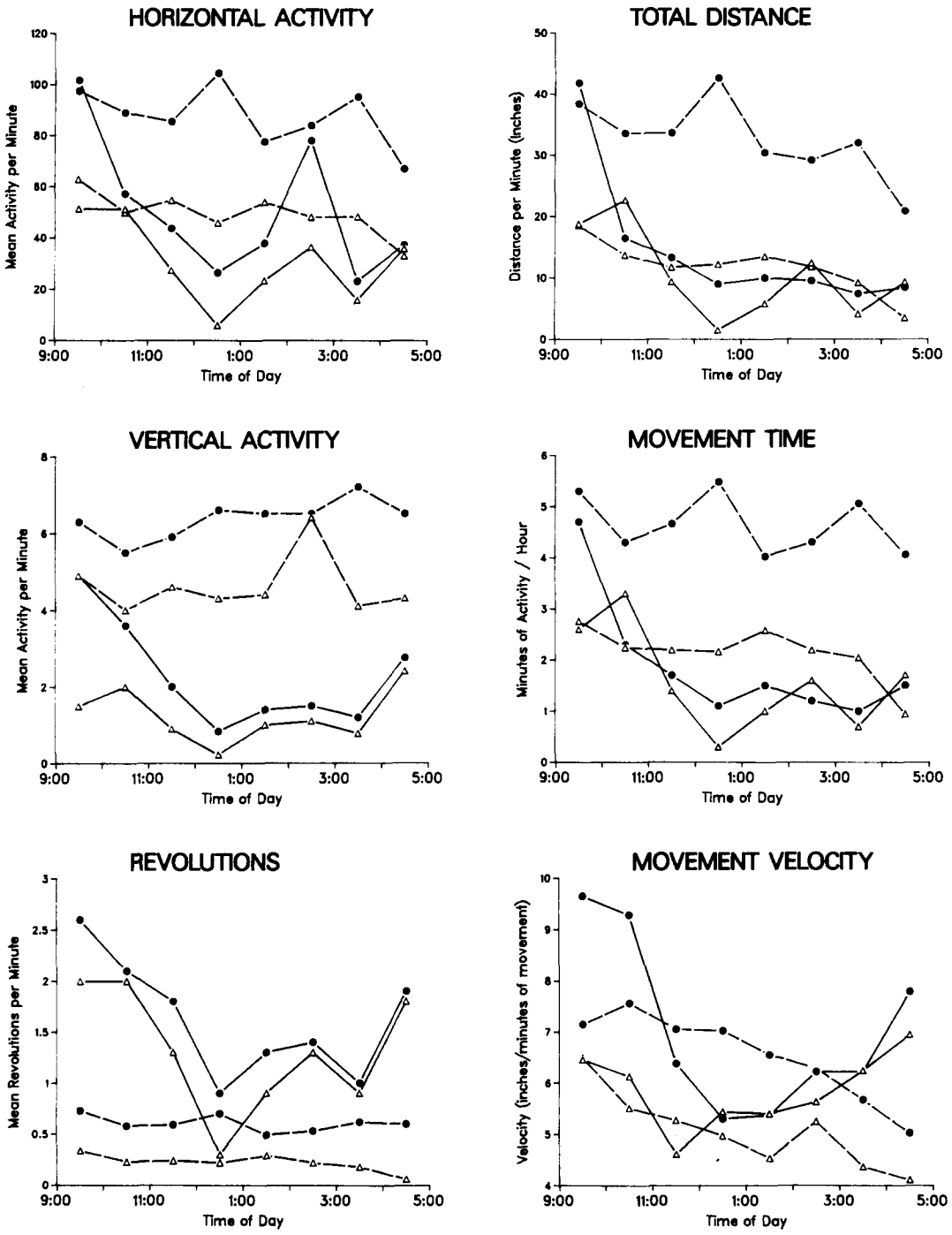

FIG. 1. Mean diurnal activity distributions for the six behavioral measures of the LMA of NBM and OC rats. The vertical axes present the mean measure of activity. The horizontal axes present the time-of-day in hours, where day (0900–1700 hr) and night (2100–0500 hr) are superimposed and expressed in clock time (9:00–5:00 a.m. and p.m.). △——△: OC-Day; △— —△: OC-Night; ●——●: NBM-Day; ●— —●: NBM-Night.

MA). At each test session, two NBM and two OC rats were evaluated simultaneously, in individual Digiscan monitors, on six LMA variables: horizontal activity, vertical activity (rearing), total distance travelled, movement time, movement velocity (total distance travelled/movement time), and revolutions (clockwise and anticlockwise turning).

One month after surgery, half the rats were sacrificed by decapitation and the brains were removed and assayed for choline acetyltransferase (ChAT) activity [7] and high affinity choline uptake (HACU, modified from 10) in frontal cortex.

TABLE 1

STATISTICAL COMPARISONS OF DAY AND NIGHT LOCOMOTOR ACTIVITY FOLLOWING LESIONS OF THE NUCLEUS BASALIS MAGNOCELLULARIS

	F Values[a]			Time of Day							
LMA Variable	Condition[b]	Time[c]	Interaction[c]	9:00–10:00	10:00–11:00	11:00–12:00	12:00–1:00	1:00–2:00	2:00–3:00	3:00–4:00	4:00–5:00
Horizontal Activity											
DAY: NBM vs. OC	2.19	15.31†	0.35								
NIGHT: NBM vs. OC	7.22†	7.90†	1.28				*			*	*
NBM: DAY vs. NIGHT	0.53	3.76†	5.33†			*	*			*	
OC: DAY vs. NIGHT	0.01	14.34†	12.92†				*			*	
Vertical Activity											
DAY: NBM vs. OC	1.94	13.89†	0.60								
NIGHT: NBM vs. OC	2.39	2.56†	0.53								
NBM: DAY vs. NIGHT	6.19†	2.59†	4.36†			*	*	*	*	*	
OC: DAY vs. NIGHT	13.34†	3.35†	5.80†	*		*	*	*	*	*	
Total Distance											
DAY: NBM vs. OC	0.49	16.75†	0.40								
NIGHT: NBM vs. OC	11.83†	9.33†	1.64	*	*	*	*		*	*	*
NBM: DAY vs. NIGHT	1.09	4.20†	4.97†			*	*		*	*	
OC: DAY vs. NIGHT	2.71	17.95†	15.46†				*				*
Movement Time											
DAY: NBM vs. OC	0.06	19.99†	0.41								
NIGHT: NBM vs. OC	9.90†	8.17†	1.03	*		*	*		*	*	*
NBM: DAY vs. NIGHT	3.21	3.67†	6.31†			*	*		*	*	*
OC: DAY vs. NIGHT	1.06	15.66†	15.95†				*			*	
Movement Velocity											
DAY: NBM vs. OC	0.88	1.17	0.36								
NIGHT: NBM vs. OC	7.69†	7.18†	0.74		*	*	*	*		*	
NBM: DAY vs. OC	0.18	1.13	0.60								
OC: DAY vs. NIGHT	3.55	2.39†	7.23†								*
Revolutions											
DAY: NBM vs. OC	1.24	10.69†	0.54								
NIGHT: NBM vs. OC	11.85†	5.05†	0.97	*		*	*		*	*	*
NBM: DAY vs. NIGHT	0.28	2.83†	3.93†			*	*		*		*
OC: DAY vs. NIGHT	2.13	15.01†	15.01†			*					*

[a]Two-factor analysis of variance with repeated-measures on the time factor.
[b]$df = 1,22$.
[c]$df = 1,176$.
†$p<0.05$.
*Post-hoc Scheffe contrasts significant at $p<0.05$.

RESULTS

There were no differences between the NBM and OC groups during the day (0900–1700 hr) in any of the six LMA variables (see Fig. 1 and Table 1) as determined by two-factor analysis of variance with repeated measures on the time factor [12]. At night (2100–0500 hr), however, NBM LMA was greater than OC LMA for all variables except vertical activity, which was consistently high in both groups throughout the night. Both during the day and the night, there were significant within-subjects variations in activity over time for all LMA variables except daytime movement velocity, which indicates that activity was not constant throughout the diurnal cycle. There were, however, no significant interaction effects, which indicates that the activity patterns of the NBM and OC groups were similar. For each LMA variable, the between-subjects variations (i.e., the comparison of the NBM and OC surgery conditions, and of the night and day conditions) were analyzed by post-hoc Scheffe contrasts on the repeated measure (see Table 1).

For both the NBM and OC groups, there were no significant group differences between night and day LMA except that vertical activity was higher at night. There were, however, significant within-subject variations over time, accompanied by significant interaction effects, which indicate that night LMA patterns were different than the day patterns (see Table 1 for post-hoc comparisons). The exception was that NBM movement velocity showed no statistical variation over time either during the day or night.

NBM lesions significantly decreased ChAT activity in frontal cortex by 33%, and high affinity choline uptake by 34%, as compared to the corresponding cortical region in OC

rats (both $p<0.05$, two-tailed Student's t-test). One NBM rat, that showed no deficit in cortical ChAT activity or HACU, was excluded from the above LMA analysis.

DISCUSSION

The NBM lesion did not significantly alter the daytime levels of any of the six behavioral measures of LMA, although, as one might expect, both NBM and OC rats were more active at night. NBM rats spent more time at night moving than OC rats, they also traversed more distance with greater velocity and turned more. Vertical activity, a measure of rearing, was not influenced by NBM lesions, during the day or night, thus supporting the notion that rearing behavior is associated with different neural substrates than ambulation [8].

The distributions of horizontal activity, distance travelled and movement time appeared to have covarying patterns, particularly during NBM LMA at night. The increased movement time and distance travelled indicate that horizontal activity represented actual ambulation and not repeated bouts of stationary stereotypy. During the day, the distributions for turning (revolutions) and for horizontal and vertical activity suggest cyclical and bimodally-distributed patterns in the OC group that are not apparent at night. These patterns also were observed in the NBM group, which suggests that the NBM lesions affected neither the magnitude nor the distribution of diurnal LMA.

Although there were no statistically significant differences between OC and NBM rats in any daytime LMA, Fig. 1 shows that NBM activity was elevated in several LMA variables for the first, and often the second, hour of daytime measurements while NBM activity during subsequent hours was comparable to OC activity. The initially high level of NBM activity may have been a reaction to the novel environment of the LMA cage. As such, these data support the idea that apparent NBM hyperactivity, observed in other LMA studies, may simply reflect slower habituation to a novel environment [7]. It remains unclear, however, why this effect was observed only during the day. Perhaps because the LMA of both NBM and OC groups was high throughout the night, any initial elevation of activity may have been obscured.

The present experiment provides a detailed analysis of NBM lesion effects on six LMA variables measured simultaneously throughout the diurnal cycle. Because NBM lesions do not significantly alter LMA during the day, when laboratory rats are usually tested, hypotheses regarding lesion-induced hyperactivity cannot fully account for impaired performance on tasks which are designed to measure learning and memory. While we have not ruled out other possible confounding factors, our conclusion supports a growing body of evidence that the behavioral deficits observed following NBM lesions may be produced by a specific impairment of learning and memory.

REFERENCES

1. Black, A. H., L. Nadel and J. O'Keefe. Hippocampal function in avoidance learning and punishment. *Psychol Bull* **84:** 1107–1129, 1977.
2. Eichelman, B. S. Effect of subcortical lesions on shock-induced aggression in the rat. *J Comp Physiol Psychol* **74:** 331–339, 1971.
3. Friedman, E., B. Lerer and J. Kuster. Loss of cholinergic neurons in the rat neocortex produces deficits in passive avoidance learning. *Pharmacol Biochem Behav* **19:** 309–312, 1983.
4. Glick, S. D. and S. Greenstein. Comparative learning and memory deficits following hippocampal and caudate lesions in mice. *J Comp Physiol Psychol* **82:** 188–194, 1973.
5. Hepler, D. J., D. S. Olton, G. L. Wenk and J. T. Coyle. Lesions in the nucleus basalis magnocellularis and medial septal area of rats produce qualitatively similar memory impairments. *J Neurosci* **5:** 866–873, 1985.
6. Hepler, D. J., G. L. Wenk, B. L. Cribbs, D. S. Olton and J. T. Coyle. Memory impairments following basal forebrain lesions. *Brain Res* **346:** 8–14, 1985.
7. Lerer, B., J. Warner, E. Friedman, G. Vincent and E. Gamzu. Cortical cholinergic impairment and behavioral deficits produced by kainic acid lesions of rat magnocellular basal forebrain. *Behav Neurosci* **99:** 661–667, 1985.
8. Sanberg, P. R., T. H. Moran, L. L. Kubos and J. T. Coyle. Automated measurement of rearing behavior in adult and neonatal rats. *Behav Neurosci* **98:** 743–746, 1984.
9. Sanberg, P. R., M. A. Henault and A. W. Deckel. Locomotor hyperactivity: Effects of multiple striatal transplants in an animal model of Huntington's disease. *Pharmacol Biochem Behav* **25:** 297–300, 1986.
10. Simon, J. R., S. Atweh and M. J. Kuhar. Sodium-dependent high affinity choline uptake: a regulatory step in the synthesis of acetylcholine. *J Neurochem* **26:** 909–922, 1976.
11. Teitelbaum, H. and P. Milner. Activity changes following partial hippocampal lesions in rats. *J Comp Physiol Psychol* **56:** 281–289, 1963.
12. Winer, B. J. *Statistical Principles in Experimental Design*, 2nd edition. New York: McGraw-Hill, 1971, pp. 518–539.